Spatial genetics: a methodological overview

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Outline

Introduction

Testing spatial structures
  Moran’s Index
  Mantel’s correlation
  Correlogram

Multivariate analysis and spatial patterns

Inferring directionality
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Multivariate analysis and spatial patterns

Inferring directionality
Island model

Reproduction within populations + migration.
Hierarchical island model

Reproduction within subpopulations + stratified migration.
Isolation by distance (IBD)

Reproduction between neighbours → 'diffusion' of genes

Population A

Gene flow (diffusion)

Population B
Inbreeding avoidance

Mating with individuals from another population → 'repulsion' structure
Genetic models and spatial structures

- *island / hierarchical island model*: patches of related genotypes
- *isolation by distance (IBD)*: clines of genetic differentiation
- *inbreeding avoidance*: repulsion structure

⇒ Genetic processes often create spatial structures.
Genetic models and spatial structures

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⇒ Genetic processes often create spatial structures.
Using spatial information in genetic data analysis

- test the existence of spatial patterns
- detect the scales of spatial structures
- describe spatial genetic structures
- infer directionality of the patterns (migrations)
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Inferring directionality
Spatial autocorrelation

Definitions:

- *in general*: values of a variable non independent from the corresponding spatial locations
- *in genetics*: genetic distance is correlated to spatial distance

Two types of spatial autocorrelation:

- *positive*: closer individuals are more similar than at random
- *negative*: closer individuals are more dissimilar than at random
Spatial autocorrelation

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Two types of spatial autocorrelation:

- *positive*: closer individuals are more similar than at random
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Spatial autocorrelation: illustration

- Positive autocorrelation
- No autocorrelation (random)
- Negative autocorrelation
Spatial weights and the lag vector

Matrix of spatial weights $L$

Row $i$: uniform weights for neighbours of $i$.

Let $x$ be a variable with one value at each location.

The lag vector $Lx$ computes mean values of neighbours.
Spatial weights and the lag vector

Matrix of spatial weights $L$

Row $i$ : uniform weights for neighbours of $i$.

```
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   c  0.000 0.000 0.000 1.000 0.000
   d  0.000 0.333 0.333 0.000 0.333
   e  0.333 0.333 0.000 0.333 0.000
```

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Let $x$ be a variable with one value at each location.

The lag vector $Lx$ computes mean values of neighbours.
A variable and its lag-vector

Lag vector:

Random:

Regression of $L_x$ onto $x$: 
A variable and its lag-vector

Lag vector:

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Regression of $L_x$ onto $x$:

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A variable and its lag-vector

Positive autocorrelation:

Regression of \( L_x \) onto \( x \):

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A variable and its lag-vector

Lag vector:

Negative autocorrelation:

Regression of $L_x$ onto $x$:

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Moran’s index: definition

Moran’s $I$:

$$I(x) = \frac{x^T L x}{n} \frac{1}{\text{var}(x)}$$

where:

- $x \in \mathbb{R}^n$: a centred variable (e.g. allele frequency, PC)
- $L$: matrix of spatial weights ($n \times n$)
- $Lx$: lag vector
- $I_0 = \frac{-1}{n-1} \approx 0$: null value (no autocorrelation, i.e. random spatial distribution)

$\Rightarrow$ Moran’s $I$ varies like $\langle x, Lx \rangle$. 
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Variable, lag-vector, Moran’s $I$

Lag vector:

Random:

Moran’s $I$: 

$\begin{bmatrix} 1 & 0 & 1 & 0 & 1 \\ 0 & 1 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 1 \\ 0 & 1 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 1 \end{bmatrix}$

$I(x) \approx \frac{17}{49}$
Variable, lag-vector, Moran’s $I$

Lag vector:

Random:

Moran’s $I$:

$I(x) \approx I_0$
Variable, lag-vector, Moran’s $I$

Positive autocorrelation:

Moran’s $I$:

$I(x) > I_0$
Variable, lag-vector, Moran’s $I$

Negative autocorrelation:

Moran’s $I$:
$I(x) < I_0$
Testing Moran’s $I$

Monte Carlo procedure:

- compute $I$ from the data
- permute randomly the locations to get a value of $I$ under $H_0$: “$x$ is distributed at random across space.”
- repeat this operation a large number of times to obtain a reference distribution of $I$ under $H_0$
- compare initial value to the reference distribution to get a $p$-value.
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Application: testing spatial structures in principal components

Data (2 population, island model):

PCA results, PC 1:
Application: testing spatial structures in principal components

PCA results, PC 1:

Moran’s $I$ test of PC1:
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Multivariate analysis and spatial patterns

Inferring directionality
Univariate /vs/ multivariate correlation

- Moran’s $I$ is univariate
  - solution: test a few principal components
  - problems:
    - does not use all the genetic information
    - which PC to test?
    - correction for multiple testing

⇒ need for multivariate tests
Univariate /vs/ multivariate correlation

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$\Rightarrow$ need for multivariate tests
Mantel’s correlation: rationale

Correlation between two unfolded distance matrices.
Mantel’s correlation: definition

Notations:

- $\mathbf{X} = [x_{ij}]$ ($\mathbf{X} \in \mathbb{R}^{n \times n}$): genetic distances
- $\mathbf{Y} = [y_{ij}]$ ($\mathbf{Y} \in \mathbb{R}^{n \times n}$): geographic distances
- $\overline{x}$, $\overline{y}$: means of $x$ and $y$ (excepting diagonals)
- $s_x$, $s_y$: standard deviation of $x$ and $y$ (excepting diagonals)

Original definition (unstandardized):

$$z_M = \left( \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} x_{ij} y_{ij} \right)$$
Mantel’s correlation: definition

Notations:

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- \( Y = [y_{ij}] \ (Y \in \mathbb{R}^{n \times n}) \): geographic distances
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- \( s_x, s_y \): standard deviation of \( x \) and \( y \) (excepting diagonals)

Standardized coefficient (true correlation):

\[
\hat{r}_M = \frac{1}{d-1} \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \left( \frac{x_{ij} - \bar{x}}{s_x} \right) \left( \frac{y_{ij} - \bar{y}}{s_y} \right)
\]
Testing Mantel correlation

Monte Carlo procedure:

- compute $z_M$ or $r_M$ from the data
- permute randomly the rows and columns of one matrix, recompute the test statistic (i.e., under $H_0$: ”no correlation”)
- repeat this operation many times to generate a reference distribution
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Application: testing spatial structures

Data (2 population, island model):

Mantel test:

Histogram of sim

Frequency

Mantel correlation
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Inferring directionality
Spatial dependence at different scales

Positive autocorrelation can indicate different patterns

⇒ How to detect the scale of spatial structures?
Spatial dependence at different scales

Positive autocorrelation can indicate different patterns

⇒ How to detect the scale of spatial structures?
Correlogram: rationale

Compute spatial autocorrelation (Moran’s $I$, Mantel’s $r_M$) for different distance classes.

Approach:

- define several classes of geographic distances
- for each class, define connectivity between locations
- set spatial weights of non-connected locations to zero
- compute spatial autocorrelation for each class
Correlogram: rationale

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Correlogram: rationale

- Autocorrelation - Large scale
- Autocorrelation - Medium scale
- Autocorrelation - fine scale

Distance classes
Application: describing spatial structures

Data (2 population, island model):

Mantel correlogram:
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Inferring directionality
Mapping principal components

Maps of the three first principal components of PCA.

Is this appropriate?
Mapping principal components

Maps of the three first principal components of PCA.

Is this appropriate?
Rationale of multivariate analyses (recall)

Finding the directions summarizing best the **genetic diversity**.

Spatial information is not taken into account.
Rationale of multivariate analyses (recall)

Finding the directions summarizing best the genetic diversity.

Spatial information is not taken into account.
Using spatial information

- usual multivariate analyses ignore spatial information
- they may reveal obvious spatial structures, but overlook finer patterns
  ⇒ need for taking spatial information into account
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Spatial Principal Component Analysis (sPCA): rationale

Principal components $\mathbf{Xu}$ should:

- display \textit{variability} $\Rightarrow \max \ \text{var}(\mathbf{Xu})$
- display \textit{positive autocorrelation} $\Rightarrow \max \ I(\mathbf{Xu})$
- (or) display \textit{negative autocorrelation} $\Rightarrow \min \ I(\mathbf{Xu})$
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- display **positive autocorrelation** ⇒ $\max I(Xu)$
- (or) display **negative autocorrelation** ⇒ $\min I(Xu)$
Formalization of the problem

Notations:

- \( \mathbf{X} \): matrix of centered (possibly scaled) allele frequencies \((\mathbf{X} \in \mathbb{R}^{n \times p})\)
- \( \mathbf{L} \): matrix of spatial weights \((\mathbf{L} \in \mathbb{R}^{n \times n})\)
- \( \mathbf{u} \): principal axis made of \( p \) loadings \((\mathbf{u} \in \mathbb{R}^{p}, \|\mathbf{u}\|^2 = 1)\)
- \( \mathbf{Xu} \): principal component

The criterion of the sPCA is:

\[
g : \mathbb{R}^{n \times p} \times \mathbb{R}^{n \times n} \times \mathbb{R}^{p} \rightarrow \mathbb{R}
\]

\[
g(\mathbf{X}, \mathbf{L}, \mathbf{u}) = \text{var}(\mathbf{Xu})I(\mathbf{Xu})
\]

Additional constraints:

- \( \|\mathbf{u}\|^2 = 1 \)
- successive axes must be orthogonal
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\[
(X, L, u) \rightarrow g(X, L, u) = \text{var}(Xu)I(Xu)
\]

Additional constraints:

- \(\|u\|^2 = 1\)
- successive axes must be orthogonal
Solution

• It can be shown that:

\[ g(X, L, u) = \frac{1}{2n} u^T X^T (L + L^T) X u \]

where \( X^T (L + L^T) X \) is symmetric.

• The extremums of \( g(X, L, u) \) are then given by the eigenanalysis of:

\[ \frac{1}{2n} X^T (L + L^T) X \]

• We obtain a set of orthonormal eigenvectors \( \{u_1, \cdots, u_r\} \) associated to \( r \) non-null eigenvalues \( \{\lambda_1, \cdots, \lambda_r\} \) (with \( \lambda_i > \lambda_{i+1}, \)
\( i = 1, \ldots, r - 1 \)) verifying:

\[ \lambda_r = \text{var}(Xu_r) I(Xu_r) \leq g(X, L, u_i) \leq \text{var}(Xu_1) I(Xu_1) = \lambda_1 \]
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Spatial Principal Component Analysis (sPCA): outputs
Spatial Principal Component Analysis (sPCA): example

Chamois (*Rupicapra rupicapra*) in the Bauges mountains.

What is the genetic structure of this population (reproduction units)?
Spatial Principal Component Analysis (sPCA): example

Chamois (*Rupicapra rupicapra*) in the Bauges mountains.

What is the genetic structure of this population (reproduction units)?
Spatial Principal Component Analysis (sPCA): example

PCA results: no spatial structure, 4 outliers
Spatial Principal Component Analysis (sPCA): example

sPCA results: several spatial structures (confirmed by field observations).
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Inferring directionality
Multivariate method do not infer directionality

Principal Components have no direction.

(Cavalli-Sforza et al. 1993, Science)

How to infer migrations?
Multivariate method do not infer directionality

Principal Components have no direction.

(Cavalli-Sforza et al. 1993, *Science*)

How to infer migrations?
The 'bottleneck' effect

Original population

migration

New population

population growth
Effects of successive bottlenecks

Progressive loss of genetic diversity within populations.
Expected patterns of migrations

Diversity within population decreases with distance from the origin
Patterns of migrations: example

Reconstructing the spread of Malaria worldwide.

(Tanabe et al. 2010, Current Biology)

*Plasmodium falciparum* accompanied Human migrations.